Synthesis and application of flavin based oxidation catalysts

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CHAPTER 4

Flavin catalysts as electron transfer mediators

Apart from biocatalysis, very few organic reactions are known in which a flavin acts as an electron transfer mediator (ETM). The most striking example known is the application of a flavin catalyst as ETM in osmium catalysed cis-dihydroxylations. In this chapter the application of flavins as ETMs in oxidation reactions is described.

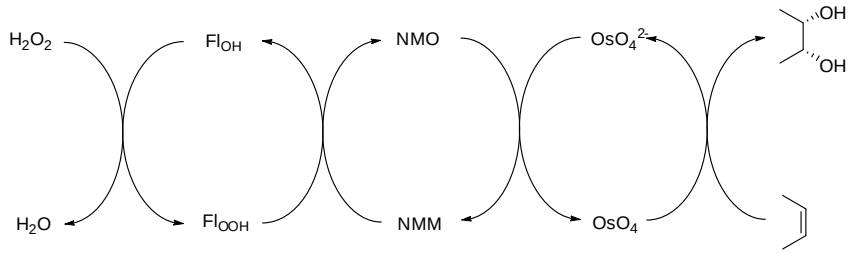
4.1 Introduction

Oxidation reactions are of fundamental importance in nature, and are key transformations in organic synthesis.[1] The development of new processes that employ transition metals as substrate-selective catalysts in combination with stoichiometric environmentally friendly oxidants, such as molecular oxygen or hydrogen peroxide, is one of the most important goals in oxidation chemistry.

The use of hydrogen peroxide or dioxygen in oxidation reactions has many advantages compared to other oxidants. Not only is hydrogen peroxide relatively safe and cheap and the active oxygen content is high, it is also clean, since the byproduct formed is water. A review detailing these reactions is available.[2] Homogeneous catalysts based on Mn,[3] Fe,[4] V,[52b], Cu,[6] Se,[7] As,[8] Mo,[9] Re,[10] Pt,[11] Zr,[12] or soluble acids[13] and heterogeneous catalysts containing As,[14] or Se,[15] titanium silicalite,[16] or solid acids[17] have been used successfully in combination with H_2O_2. Preferentially, of course, non-toxic metals are used. However even then, there are often several drawbacks, such as low activity or selectivity of the catalyst, high cost of the catalyst, or the need for anhydrous hydrogen peroxide. Furthermore, direct oxidation of a catalyst by molecular oxygen or hydrogen peroxide is often kinetically unfavourable. Each of the different catalytic systems has its advantages and disadvantages and no catalytic system can be seen as the best. The use of coupled catalytic systems with electron-transfer mediators (ETMs) can facilitate the oxidations by transporting the electrons from the catalyst to the oxidant along a low-energy pathway, which increases the efficiency of the oxidation and thus complements the direct oxidation reactions. As a result of the similarities with biological systems, this can be dubbed a biomimetic approach.[18] In the following paragraphs, a number of systems is described in which flavins are applied successfully as ETMs.

4.1.1 Osmium catalyzed cis-dihydroxylations utilizing a NMO-flavin ETM

A good example of an ETM is the osmium-catalyzed cis-dihydroxylation of carbon–carbon double bonds with flavin and N-methylmorpholine (NMM).[20] Although the osmium based cis dihydroxylation reaction works quite well with a stoichiometric amount of osmium, this is not favourable due to the high toxicity of osmium. The Upjohn procedure, in which NMO is used as the terminal oxidant and osmium can be used in catalytic quantities, is a significant improvement.[19] While NMM can be slowly oxidized to NMO using hydrogen peroxide, or more rapidly with *m*-CPBA, the group of Bäckvall *et al.* showed in 1998 that catalytic oxidation of NMM to NMO could be performed quite efficiently by either O_2 or H_2O_2 with a flavin catalyst.[20] In 2001, Bäckvall *et al.* showed that a the combination of catalytic amount of a flavin based catalyst and NMO as ETM could be used for the reoxidation of Os(VI) to Os(VIII) by H_2O_2. It was furthermore shown that the system could be employed for asymmetric dihydroxylation of alkenes.



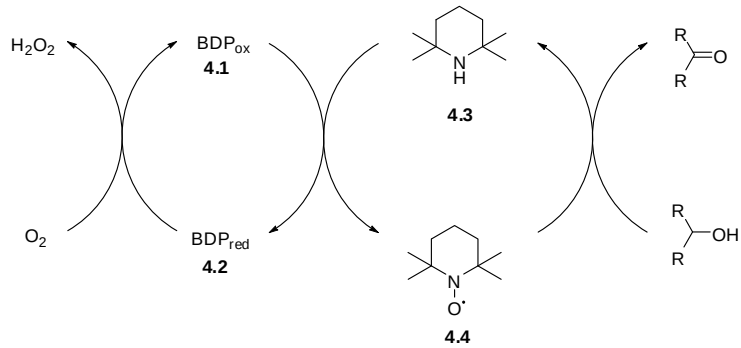
Scheme 4.1 Application of flavin catalysts as ETMs in the osmium based cis dihydroxylation.

4.1.2 TEMPO regeneration with a benzo-dipteridine

4.1 BDP_{ox} **4.2** BDP_{red}

Figure 4.1 Benzo-dipteridine (BDP_{ox}) and its $2e^-$ reduced state BDP_{red}

Benzo-dipteridine (BDP_{ox}) (**4.1**), was initially investigated as a mimic in models of flavin-mediated oxidations. Yano *et al.* looked into the activity of **4.1** in oxidative dealkylation of N-nitrosamine derivatives,[21] oxidation of sulfite ion[22] and oxidations of o-aminophenols.[23] It was found that **4.1** could oxidise N-hydroxylamines via a two-electron oxidation, which led to an investigation into the oxidation of 4-methoxy-2,2,6,6-tetramethylpiperidine (TMP, **4.3**) to its corresponding N-oxoaminium ion (**4.4**) and subsequent application of **4.1** in alcohol oxidations.[24]



Scheme 4.2 Application of BDP for in situ regeneration of TEMPO in alcohol oxidations.

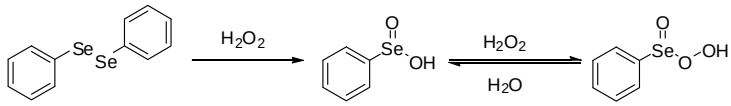
4.1.3 Regeneration of IBX

Another oxidation catalyst that is applied for selective oxidations is 2-iodoxybenzoic acid (IBX). This periodinane is especially suited for the oxidation of alcohols to aldehydes. IBX is prepared from 2-iodobenzoic acid, potassium bromate and sulfuric acid. Frigerio and co-workers demonstrated in 1999 that potassium bromate can be replaced by commercially available Oxone®.[25] However, one of the

main drawbacks of IBX is its limited solubility; IBX is insoluble in many common organic solvents. In 2001, K.C. Nicolaou and co-workers published a series of papers demonstrating, among other transformations, the use of iodine reagents in organic synthesis.[26] Moorty *et al.* published the use of IBX in combination with dimethyl sulfoxide for the oxidative cleavage of vicinal diols to ketones.[27] Vinod and colleagues showed the in situ preparation and use of catalytic IBX in alcohol oxidations utilizing stoichiometric Oxone®.[28] A good overview of reactions using hypervalent iodine reagents in catalysis was published in 2009.[29] Since certain flavoproteins can catalyze iodide oxidation, flavin based catalysts might functions as well as ETMs in these systems.

4.1.4 Selenoxides

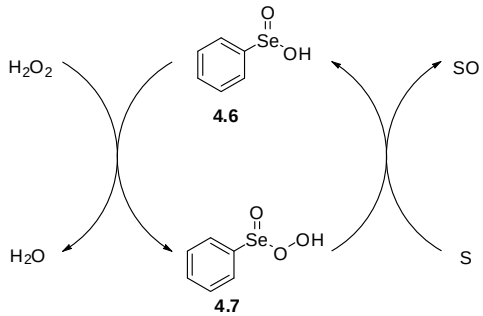
It has been shown that sulfides can be readily oxidized by hydrogen peroxide to their corresponding sulfoxides using flavin catalysts.[30] In 1982, Kuwajima *et al.* showed that diphenyldiselenides (**4.5**) could be readily oxidized to selenic acids (**4.6**), which can be converted into the selenic hydroperoxy (**4.7**) as depicted in Scheme 4.3.[33,31]



4.5 **4.6** **4.7**

Scheme 4.3 Formations of selenic hydroperoxy from diphenyldiselenides with HO_2.

Among the first catalysts, used for the epoxidation and Baeyer-Villiger reactions with H_2O_2, were substituted benzeneseleninic acids as reported by Syper.[32] The group of Sheldon investigated the effect of substituents on the aromatic diselenide in oxidation reactions. They showed that aromatic selenides can be used as catalysts in olefin epoxidations,[33] Baeyer-Villiger oxidation[34] and alcohol oxidations,[35,36] with hydrogen peroxide or *t*-butyl hydroperoxide as terminal oxidants.



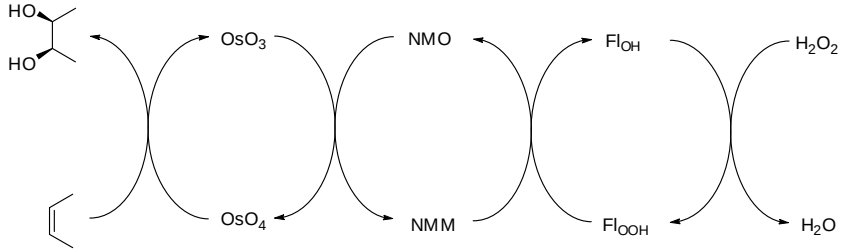
Scheme 4.4 Oxidations with hydrogen peroxides and selenic acid as catalyst.

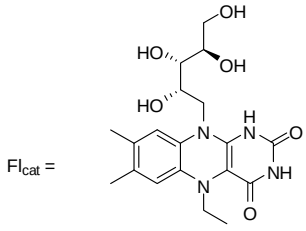
4.2 Osmium catalyzed cis-hydroxylation utilizing a NMO-flavin ETM

Since the riboflavin based catalyst **4.8** described in chapter 2 is easily accessible, its activity in the osmium based cis dihydroxylation reaction was investigated. The dihydroxylation reaction was performed on a selection of

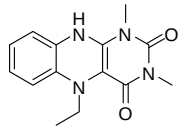
substrates, based upon the work of Bäckvall *et al.* wherein the flavin catalyst **4.9** was applied.

Table 4.1 Osmium based cis dihydroxylation reaction with a flavin ETM.

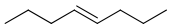
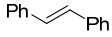




4.8



4.9

Entry	Substrate	NMM	TEAA	Flavin	Conversion	Selectivity
1					Full	51%
2		0.14 mmol	1 mmol		28 %	90%
3		0.14 mmol	1 mmol	5%	65 %	81%
4			1 mmol	5%	n.d.	87%
5					n.d.	21%
6		0.14 mmol	1 mmol		n.d.	84%
7		0.14 mmol	1 mmol	5%	n.d.	82%
8			1 mmol	5%	n.d.	75%
9					n.c.	
10		0.14 mmol	1 mmol		n.c.	
11		0.14 mmol	1 mmol	5%	n.c.	
12			1 mmol	5%	n.c.	

General condition: H_2O_2 (1.5 equiv, 77 µL, 30% aqueous) was added all at once to a mixture of the olefin (0.5 mmol) and 0.01 mmol OsO_4 (2 mol%) and the flavin based catalyst. NMM = N-methylmorpholine, TEAA = tetra ethyl ammonium acetate. Conversion of the substrate and selectivity towards the desired product were determined after 16 h. by GC-MS. n.c.= no conversion, n.d. = not determined.

Our investigation into the cis dihydroxylation reaction showed results similar to those found by the group of Bäckvall. With the addition of 1.5 equivalent of hydrogen peroxide to a mixture containing the substrate and a catalytic amount of osmium tetroxide, full conversion was observed, albeit with low selectivity to the diol. With the addition of NMM and TEAA to the reaction mixture, the selectivity went up. However, the conversion was low due to decomposition of hydrogen peroxide taking place. Intriguingly, whereas the group of Bäckvall found a large drop in yield (from 95% to 47%) in the case of trans-5-octene if no NMM was present, with our

catalyst we only observed a minor drop in selectivity, as can be observed when comparing entry 7 and 8. Further investigations into the application of the riboflavin based catalyst in catalytic osmium based cis dihydroxylation reactions are necessary to find the optimum conditions.

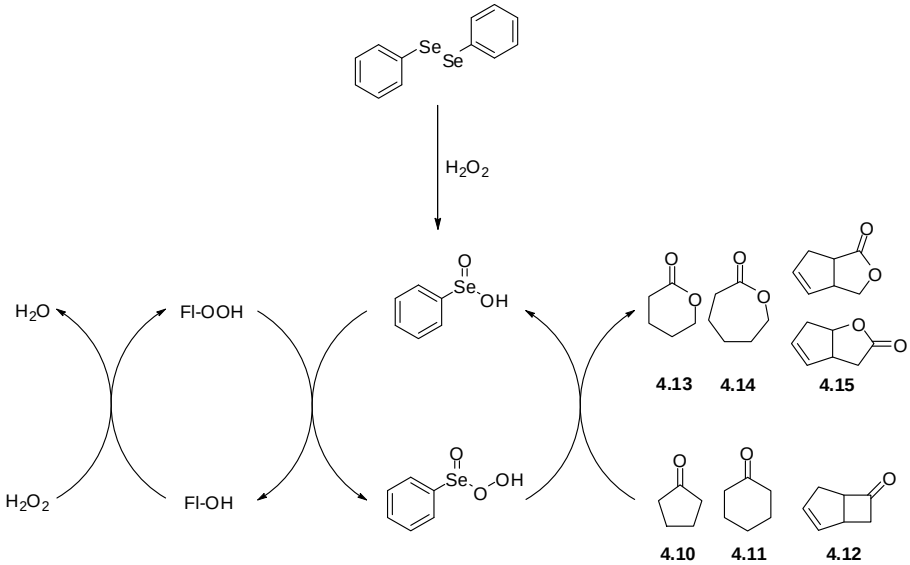
4.3 Selenium based oxidations

As shown, aromatic selenides have been shown to be active catalysts in olefin epoxidations and Baeyer-Villiger oxidations with hydrogen peroxide. The aromatic selenides proved to be easily oxidized by hydrogen peroxide in trifluoroethanol, which is akin to the oxidation of aromatic sulfides to sulfoxides. In the next paragraphs an investigation into the use of a flavin based catalyst for the regeneration of an aromatic selenium catalyst with hydrogen peroxide is described.

4.3.1 Baeyer-Villiger oxidations

As selenides can be oxidized with flavins and selenoxy hydroperoxides can be utilized in Baeyer-Villiger oxidations of ketones, we investigated if both systems could be applied in one pot yielding *in situ* regenerated selene catalyst.

Table 4.2 Se-based Baeyer-Villiger oxidations with hydrogen peroxide and riboflavin based catalyst 4.8.



Entry	Flavin	Ph_2Se_2	Solvent	substrate	Conversion
1	—	0.25 µmol	t-BuOH	**4.10**	trace
2	4 µmol	—	t-BuOH	**4.10**	trace
3	4 µmol	0.25 µmol	t-BuOH	**4.10**	trace
4	—	0.25 µmol	trifluoroethanol	**4.10**	trace
5	4 µmol	—	trifluoroethanol	**4.10**	no conversion
6	4 µmol	0.25 µmol	trifluoroethanol	**4.10**	no conversion
7	—	0.25 µmol	t-BuOH	**4.11**	no conversion
8	4 µmol	—	t-BuOH	**4.11**	no conversion
9	4 µmol	0.25 µmol	t-BuOH	**4.11**	no conversion

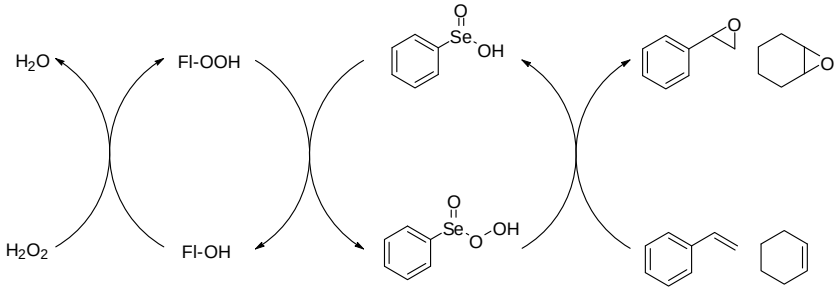
10	—	0.25 µmol	trifluoroethanol	**4.11**	no conversion
11	4 µmol	—	trifluoroethanol	**4.11**	no conversion
12	4 µmol	0.25 µmol	trifluoroethanol	**4.11**	no conversion
13	—	0.25 µmol	t-BuOH	**4.12**	94
14	4 µmol	—	t-BuOH	**4.12**	full
15	4 µmol	0.25 µmol	t-BuOH	**4.12**	89
16	—	0.25 µmol	trifluoroethanol	**4.12**	48
17	4 µmol	—	trifluoroethanol	**4.12**	64
18	4 µmol	0.25 µmol l	trifluoroethanol	**4.12**	77

General conditions: H_2O_2 (1.5 equiv, 400 µL, 30% aqueous) was added all at once to a mixture of the ketone (0.2 mmol), 4 µmol of flavin based catalyst and 0.25 µmol of diselenide (2 mol%). Conversion towards the desired products was determined after 16 hours by GC-MS analysis.

As in entry 1-4 only a trace amount of the desired product was detected, no conclusion can be drawn other than that the oxidation of cyclopentanone and cyclohexanone proved to be too difficult. However, the oxidation of the bicyclic strained ketone went quite well. Intriguingly, in *tert*-butanol, the oxidation went to full completion with solely the flavin catalyst present, while in trifluoroethanol, the combination of both catalysts proved to the best choice. Therefore, it might be worthwhile to study this reaction further with only flavin based catalysts and H_2O_2.

4.3.2 Epoxidations

Investigation of the epoxidation of carbon-carbon double bonds with aromatic selenides and flavin **4.8** and **4.9** were performed in both *tert*-butanol and trifluoroethanol, with cyclohexene and styrene as benchmark substrates.



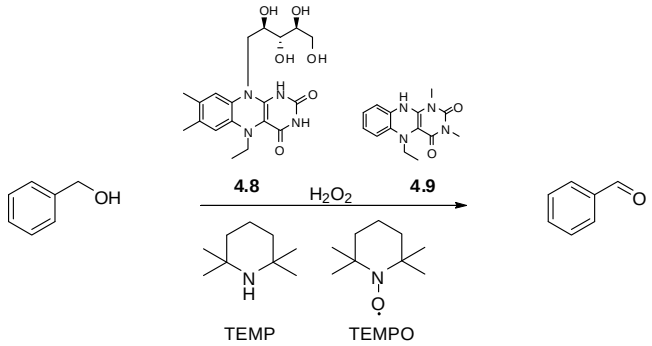
General conditions: H_2O_2 (1.5 equiv, 400 µL, 30% aqueous) was added all at once to a mixture of the olefin (0.2 mmol), 4 µmol of flavin based catalyst and 0.25 µmol of diselene (2 mol%). Conversion and selectivity were determined after 16 hours by GC-MS.

Disappointingly, no conversion was detected in any of the reaction mixtures. Just as in the case of the Baeyer-Villiger oxidations, it might be worthwhile to investigate the reactions again with a more active selenium catalyst, as has been used in the group of Sheldon, where the epoxidation reaction was performed successfully.

4.4 Results of investigations into alcohol oxidation via TEMPO regeneration

Since the dipteridine **4.2** showed promising activity with in situ regeneration of TEMPO in alcohol oxidations, this was also tested with the two most active flavin catalysts **4.8** and **4.9**. While in the oxidation of TEMP with BDP_{ox} it is presumed that the TEMP forms an adduct with BDP_{ox}, which is oxidized by O_2, catalysts **4.8** and **4.9**

are easily oxidized by hydrogen peroxide and can form a hydroperoxy species. Alternatively, instead of using hydrogen peroxide, oxygen can be used as the terminal oxidant in the catalytic cycle. To achieve that aim, a reductant is necessary to obtain the state in which the flavin catalyst can undergo attack by oxygen. Possible reductants that can be utilized for this reduction are zinc and hydrazine.



Scheme 4.5 Alcohol oxidations with riboflavin based catalyst and TEMPO
General conditions: H_2O_2 (1.5 equiv, 110 µL, 30% aqueous) or zinc (65 mg) were added all at once to a mixture of the olefin (1 mmol), 1 mg of flavin based catalyst and either 10 mg of TEMP of TEMPO in 2 ml *tert*-butanol. Conversion and selectivity were determined after 16 hours by GC-MS.

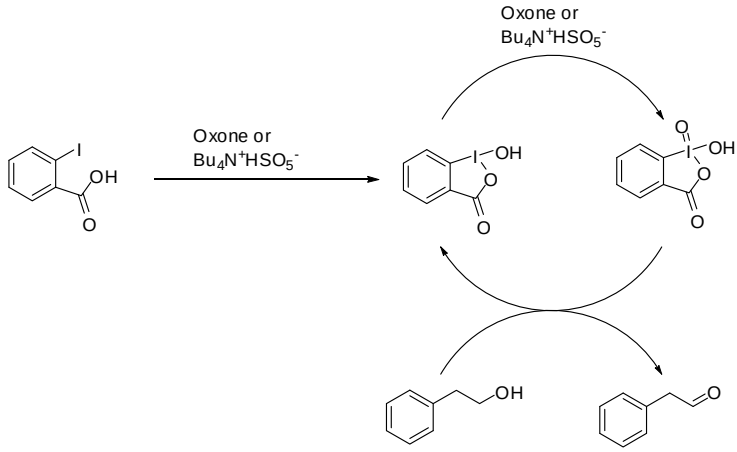
Oxidation towards the desired aldehyde was not observed in any of the cases. Intriguingly there was also no indication of the desired product in the reactions in which TEMPO was present. It was noted however, that with the addition of TEMPO to a flavin catalyst in solution, the same change in color was observed as is normally observed when hydrogen peroxide is added, indicating that it is likely that the TEMPO oxidized the flavin. In this case any TEMPO present would be reduced easily, explaining why the desired product was never observed.

It is probable that the peroxyflavins are not capable of oxidising TEMP to TEMPO. Noteworthy, however, was that with the combination of catalyst **4.8**, TEMP and zinc, the blue coloured (radical) flavin species, which is formed in H_2O did not degrade within a day, as was normally observed, but was present in the reaction mixture for at least seven days.

4.5 Investigation in *in situ* regeneration of IBX with a flavin catalyst

As flavoproteins that catalyze iodide oxidation[37] are known, we tested if our flavin catalyst can be utilized for IBX regeneration with hydrogen peroxide as the terminal oxidant.

Table 4.4 Phenylethanol oxidation with IBX in situ regenerated by a flavin based catalyst.



entry	solvent	Fl cat (mg)	iodide species	H_2O_2 (µl)	yield
1	t-BuOH	**4.9** (2)	IBX	110	–
2	t-BuOH	**4.9** (2)	IBA	110	–
3	t-BuOH	**4.9** (2)	IBX	–	–
4	t-BuOH	**4.9** (2)	IBA	–	–
5	t-BuOH	–	IBX	110	–
6	t-BuOH	–	IBA	110	–
7	t-BuOH	–	–	110	trace
8	t-BuOH	**4.8** (10)	IBX	110	–
9	t-BuOH	**4.8** (10)	IBA	110	–
10	t-BuOH	**4.8** (10)	IBX	–	trace
11	t-BuOH	**4.8** (10)	IBA	–	–
12	t-BuOH	–	–	110	–
13	TFE	**4.9** (2)	IBX	110	–
14	TFE	**4.9** (2)	IBA	110	trace
15	TFE	**4.8** (10)	IBX	–	trace
16	TFE	**4.8** (10)	IBA	–	trace
17	TFE	–	IBX	110	trace
18	TFE	–	IBA	110	trace
19	TFE	–	–	110	trace
20	DMSO	–	IBX	110	trace
21	DMSO	**4.9** (2)	IBA	110	trace
22	DMSO	**4.8** (10)	–	110	trace

General conditions: to 4 ml of solvent was added, H_2O_2 (1.5 equiv., 110 µL, 30% aqueous) was added all at once to a mixture of the olefin (1 mmol), 1 mg of flavin based catalyst and 0.1 mmol of IBA (26.4 mg, 10 mol%) or IBX (26.4 mg, 10 mol%). Conversion and selectivity were determined after 16 hours with a GC-MS.

Although in some cases, a trace amount of the desired product was detected, this was at the limit of the detection with values too low to be considered as a

successful conversion. It is quite probable that the hydroperoxy species are not capable of oxidising IBA to IBX. However, in entries in which solely IBX was present a blank reactions was expected, but not observed. Therefore no conclusive facts can be drawn about the reactivity.

4.6 Conclusions

Although we investigated a number of potential reactions in which flavin based catalysts could act as electron transfer mediators (ETM), in most cases we only found trace amounts of the desired products. There is evidence that the osmium catalyzed cis-hydroxylation can be performed with only the flavin catalyst and no NMM. With a range of flavin based catalysts with different oxidation potentials, it might still be possible to find more applications in which flavins can act as ETM's.

4.7 Experimental section

General: ^{1}H-NMR spectra were recorded on a Varian 400 MHz and MeOD-d_4 as solvent. In all cases, reference compound have been injected on the GC and GC-MS to certify the products.

Osmium based cis-hydroxylations with flavin ETM
General conditions: H_2O_2 (1.5 equivalent, 77µL, 30% aqueous) was added all at once to a mixture of the olefin (0.5 mmol) and 0.01 mmol OsO_4 (2 mol%). After 16 h the reactions were quenched with $Na_2S_2O_4$ (60 mg) and Florisil (magnesium silicate) (120 mg), conversion and selectivity were determined by GC-MS.

Baeyer-Villiger oxidations with selenium and flavin based catalysts
General conditions: H_2O_2 (1.5 equivalent, 400 µL, 30% aqueous) was added all at once to a mixture of the ketone (0.2 mmol), 4 umol of flavin catalyst and 0.25 umol of diselene (2 mol%). Conversion and selectivity were determined after 16 h by GC-MS.

Epoxidation with selenium and flavin based catalysts
General conditions: H_2O_2 (1.5 equivalent, 400 µL, 30% aqueous) was added all at once to a mixture of the olefin (0.2 mmol), 4 umol of flavin catalyst and 0.25 umol of diselene (2 mol%). Conversion and selectivity were determined after 16 h by GC-MS.

Alcohol oxidations with TEMPO and flavin based catalyst
General conditions: H_2O_2 (1.5 equivalent, 110 µL, 30% aqueous) was added all at once to a mixture of the olefin (1 mmol), 1 mg of flavin catalyst and 10 mg of TEMP or TEMPO. Conversion and selectivity were determined after 16 h by GC-MS.

Alcohol oxidations with IBX and flavin based catalyst
General conditions: H_2O_2 (1.5 equivalent, 110 µL, 30% aqueous) was added all at once to a mixture of the olefin (1 mmol), 1 mg of flavin catalyst and 0.1 mmol of fresh IBA or fresh IBX (10 mol%). Conversion and selectivity were determined after 16 h by GC-MS.

4.7 References and notes

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